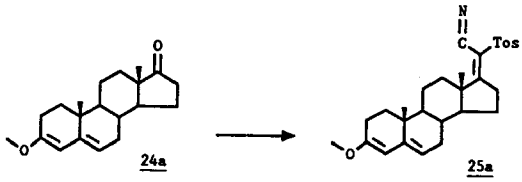
SUMMARY

This thesis describes a new method for the introduction of the corticoid side chain, the 17ß-(hydroxyacetyl) group, in 17-oxosteroids. One of the crucial and novel parts of the method is based on the use of p-toluenesulfonylmethyl isocyanide (TosMIC). Nowadays, 17-oxosteroids are attractive starting materials for the industrial preparation of corticosteroids, an important class of anti-inflammatory drugs. A number of 17-oxosteroids is readily accessible by biodegradation of plantsterols, such as the abundantly available ß-sitosterol (from soybean waste).

Chapter I gives some general information about steroids. A brief review is given of known methods for the construction of the corticoid side chain. Furthermore, a short introduction is presented on the chemistry of TosMIC and its derivatives, which plays an important role throughout this thesis.

Chapter II describes the method of introduction of the first (C-20) carbon of the corticoid side chain in 17-oxosteroids. Pinacolone has been used instead of 17-oxosteroids to study, in a model reaction, the reactivity of the 17-oxo group in relation to the properties of TosMIC. 17-Oxosteroids 24 are converted in three steps with the use of TosMIC into 17-(isocyano-tosylmethylene)steroids 25. A procedure is developed to combine the three separate steps into a one pot process, which leads to a facile and efficient conversion of 17-oxosteroids 24 into the isocyano-tosylmethylene derivatives 25. Insight into the scope and limitations of these reactions leading to compounds 25 is obtained by variation of structure and substituents of the steroids 24, and by the use of sulfonylmethyl isocyanides other than TosMIC.

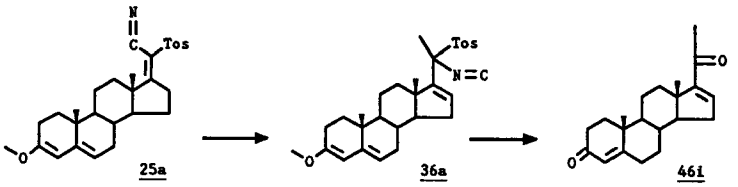
An example of the conversion of 17-oxosteroids compounds 24 to the intermediates 25



24a 25a

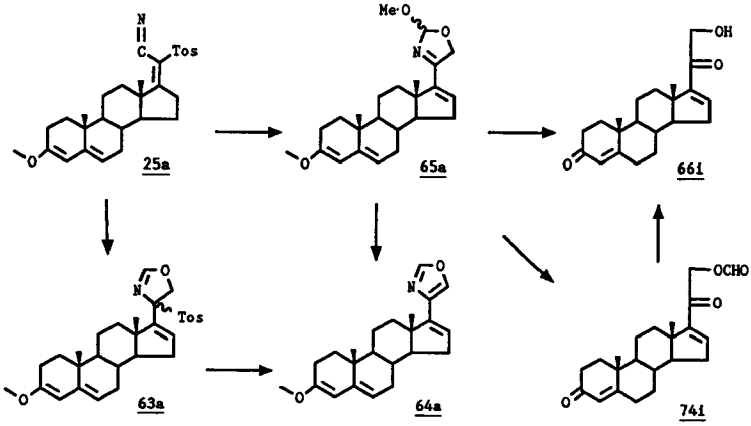
Methylation of 17-(isocyano-tosylmethylene)steroids 25, leading to 20-isocyano-20-tosylpregnenes 36, is reported in Chapter III. Hydrolysis of compounds 36 provides Δ^{16}-20-oxopregnenes 46. In addition to the methylation, halomethylation and alkoxymethylation reactions lead in a similar fashion to 21-halo and 21-alkoxy-20-oxo-Δ^{16}-pregnene derivatives 48-51.

An example of the conversion of compounds 25 to pregnenes 46



Chapter IV describes the hydroxymethylation of 17-(isocyanotosylmethylene)steroids 25 at carbon C-20 to complete the carbon skeleton of the 17β-(hydroxyacetyl) group. The initial products formed from 25 and formaldehyde are the 17-(4'-tosyl-2'-oxazolin-4'-yl)steroids 63, which are unstable. However, when the reaction is carried out in the presence of methanol compounds 63 are converted *in situ* into the stable 17-(2'-methoxy-3'-oxazolin-4'-yl)steroids 65. These oxazolines 65, which are prepared in high yields, are excellent precursors of 21-hydroxy-20-oxosteroids 66, as well as 21-formyloxysteroids 74. 17-(Oxazol-4'-yl)steroids 64 may also be obtained from 25 and formaldehyde. As a sideline, a method was developed for the conversion of the less reactive C-17 oxazolyl group into the same corticoid side chains (as in 66i), by way of an alternative of the use of the 2'-methoxy-3'-oxazolin-4'-yl group.

Examples of the conversion of compounds 25 to the steroids derivatives 64, 66 and 74

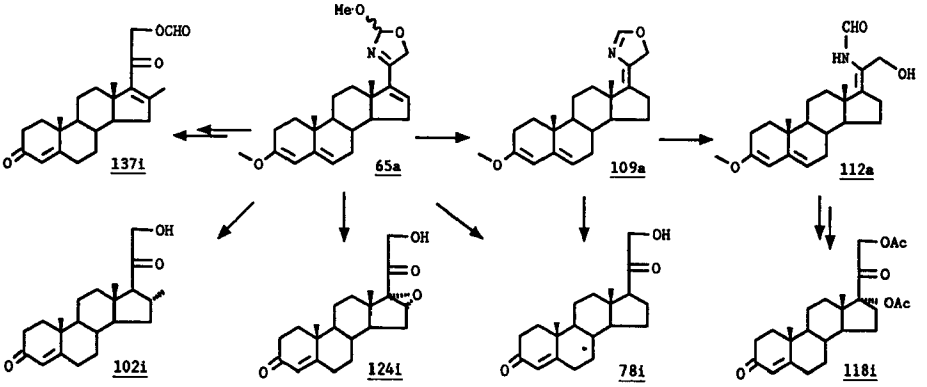


The 2-methoxy-3-oxazolin-4-yl group of 17-(2'-methoxy-3'-oxazolin-4'-yl)-Δ^{16}-steroids 65 serves as a "masked" hydroxyacetyl side chain. Chapter V deals with the chemistry of the 2'-methoxy-3'-oxazolin-4'-yl group of steroids 65, in particular with respect to the use of the hydroxy acetyl side chain as a new protective group. Examples of the effective use of this protective group are: Reaction of 65a with MeMgI and subsequent hydrolysis provides 21-hydroxy-16α-methylpregn-4-ene-3,20-dione

(102i); Oxidation of oxazoline 65a followed by hydrolysis to give 16α,17-epoxide 124i; Reduction of 65a and hydrolysis leading to 21-hydroxyprogesterone (78i).

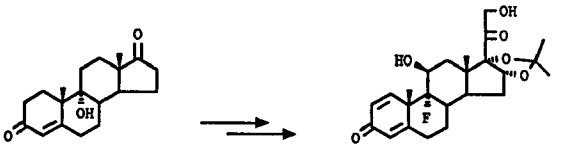
The intermediate (Z)-oxazolinylidene steroid 109a, obtained from 65a and $NaBH_4$, provides formamide 112a when treated with alumina. The synthesis of 3,20-dioxopregn-4-ene-17,21-diyl diacetate 118i from the (Z)-formamide 112a is described as well as from the (E)-formamide 113a. In addition to (Z)-109a, the (E)-isomer 110a (not depicted) has been obtained selectively by reduction of 65a with 9-BBN, instead of $NaBH_4$. Furthermore, the reaction of methoxyoxazoline 65a leading to 3,20-dioxo-16-methylprega-4,16-dien-21-yl formate (137i) is reported.

Examples of the use of the 17-(2'-methoxy-3'-oxazolin-4'-yl) ring as a protective group of the 17-hydroxyacetyl side chain



Chapter VI describes the synthesis of 16α,17α,21-trihydroxy-20-oxosteroids 143 and their C-21 formic esters 142, which are readily obtained from oxazolines 65. Finally, the synthesis of triamcinolone acetonide 151, a widely used corticoid is described. This one example was selected to show how our new reactions are incorporated elegantly into the complete conversion of the 17-oxosteroid 9α-hydroxyandrost-4-ene-3,17-dione (24y) into triamcinolone acetonide (151). The conversion of 24h into triamcinolone acetonide 151 shows the capacities of TosMIC chemistry. Core intermediates in this process are the TosMIC-derivative 25h and 9α-hydroxy-17-(2'-methoxy-3'-oxazolin-4'-yl)steroid 65h.

The starting material of this sequence of reactions, the 9α-hydroxy-AD (24h) has recently become available from Gist brocades as an industrial intermediate.



9α-hydroxy-AD 24h triamcinolone acetonide 151